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Changes in Non-high-density Lipoprotein Cholesterol Levels and Triglyceride/High-density Lipoprotein Cholesterol Ratios among Patients Randomized to Aripiprazole versus Olanzapine

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Abstract

Objective—Non-high-density lipoprotein cholesterol (non-HDL-C) and the triglyceride to high-density lipoprotein cholesterol ratio (TG:HDL-C) are predictors of cardiovascular risk. This *post-hoc* analysis assessed changes in these parameters during treatment with the atypical antipsychotics olanzapine or aripiprazole using pooled data from three randomized, long-term clinical studies in patients with schizophrenia.

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Methods—Data were pooled from one open-label and two double-blind (26- or 52-week) studies in patients randomized to olanzapine (5–20 mg/day) or aripiprazole (15–30 mg/day). Change from baseline in non-HDL-C levels between groups was analyzed in the Observed Case (OC) dataset at each time point and Last Observation Carried Forward (LOCF) dataset at endpoint using analysis of covariance, with treatment as main effect and baseline non-HDL-C as covariate. Differences between groups in median changes from baseline in TG:HDL-C were assessed with Kruskal–Wallis tests.

Results—This analysis included 546 patients (olanzapine, n=274; aripiprazole, n=272). Mean changes from baseline in non-HDL-C levels were significantly different ($p<0.0001$) with olanzapine versus aripiprazole at Weeks 26 (+13.0 vs. –7.5 mg/dL) and 52 (+12.2 vs. –8.1 mg/dL). Baseline TG:HDL-C was high in the olanzapine (3.73) and aripiprazole (3.79) groups. Differences in median changes from baseline in TG:HDL-C were significant with olanzapine versus aripiprazole at Weeks 26 (+0.22 vs. –0.54; $p<0.0001$) and 52 (+0.24 vs. –0.62; $p=0.004$).

Conclusions—Long-term aripiprazole treatment is associated with improvements in lipid profiles of schizophrenia patients versus no improvement or worsening during olanzapine treatment. Consideration of cardiovascular risk is needed when prescribing antipsychotics, as is close monitoring for metabolic changes during treatment.

Keywords

aripiprazole; olanzapine; atypical antipsychotic; non-high-density lipoprotein cholesterol; triglyceride

1. Introduction

Individuals with major mental disorders lose 25 or more years of life expectancy, with coronary heart disease (CHD) as the leading cause of death (Colton and Manderscheid, 2006; Newcomer J. W. and Hennekens, 2007). Consistent with this observation, the prevalence of key modifiable risk factors for cardiovascular disease (CVD), including both CHD and cerebrovascular disease, is increased in patients with mental disorders such as schizophrenia and bipolar disorder compared with the general population. This includes three times the prevalence of smoking (Goff et al., 2005) and 1.2- to 2-times the prevalence of obesity, dyslipidemia, hypertension and diabetes (Fagiolini et al., 2005; McEvoy et al., 2005; Newcomer J. W., 2005). The increased prevalence of CVD can be explained, in part, by under-monitoring and under-treatment of risk factors for CVD in patients with major mental disorders compared with the general population (Morrato et al., 2008; Nasrallah et al., 2006; Newcomer J. W. and Hennekens, 2007).

Growing evidence indicates that some antipsychotic treatments can further elevate CVD risk in treated individuals, via adverse effects that include weight gain, and alterations in lipid and glucose metabolism, with lipid alterations primarily being detected in the form of elevated plasma triglyceride (TG), a marker of insulin resistance (ADA/APA/AACE/NAASO, 2004; Allison et al., 1999; Koro et al., 2002; Meyer and Koro, 2004; Newcomer J. W., 2004). The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial, for example, found that olanzapine treatment was associated with the largest risk of weight gain and dyslipidemia among the antipsychotics tested, with substantial adverse effects on plasma TG (Lieberman et al., 2005; Meyer et al., 2008; Nasrallah, 2006; Stroup et al., 2006).

Various circulating lipid fractions can be used to predict CVD risk, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol and TG levels, with HDL-C and total cholesterol commonly used in risk-

estimating algorithms derived from the Framingham Heart Study (Grundy et al., 2004; NCEP, 2001). However, growing evidence indicates that the combined measure of non-high-density lipoprotein cholesterol (non-HDL-C) is a convenient and robust predictor of future CVD events and an indicator of apolipoprotein B-related risk (Sattar et al., 2004). Non-HDL-C encompasses all of the cholesterol present in TG-rich lipoprotein particles that are considered to be atherogenic – low-, intermediate- and very low-density lipoprotein cholesterol (LDL-C, IDL-C and VLDL-C, respectively) and lipoprotein(a) – and is calculated as the difference between total cholesterol and HDL-C. Although fasting LDL-C is considered to be the primary target for lipid-lowering therapy in the general population (NCEP, 2001), total fasting non-HDL-C can be a better predictor of atherosclerosis and future CHD risk than fasting LDL-C, HDL-C, or other individual lipid measures, particularly when aiming to account for the contribution of insulin resistance to dyslipidemia (Farwell et al., 2005; Frontini et al., 2007; Liu et al., 2006). This observed predictive utility of non-HDL-C has emerged in general population studies (Farwell et al., 2005; Frontini et al., 2007; Liu et al., 2006), as well as from samples of individuals with Type 2 diabetes mellitus, in whom an increase in non-HDL-C from 127 ng/dL to 156 ng/dL is associated with a 50% increase in the relative risk of CVD (Jiang et al., 2004). On a practical level, non-HDL-C measurement offers several advantages, including potential value in patients who are not fasting and in those with TG levels >400 mg/dL (Gardner et al., 2000). Non-HDL-C may therefore be an important additional tool for monitoring antipsychotic treatment-related changes in CVD risk, particularly because the adverse metabolic effects of antipsychotic treatment are largely related to adverse effects on adiposity and insulin sensitivity, with related changes in plasma TG (Lieberman et al., 2005; Newcomer J. W., 2005).

Another important application of plasma lipid markers that is relevant to schizophrenia patients is the association between the TG:HDL-C ratio and both CVD risk and insulin sensitivity. The value of high TG:HDL-C ratio for prediction of CHD risk has been seen in various studies (Jeppesen et al., 2003; McLaughlin et al., 2005) – for example, the large Copenhagen Male Study (Jeppesen et al., 2003), including 2906 men without known CHD at baseline, in which individuals with high TG and low HDL-C levels had a significantly elevated risk for fatal ischemic heart disease compared with all other participants.

Decreased sensitivity to tissue insulin action – insulin resistance – has been observed to be a key contributor to CHD risk, which underlies the public health interest in the metabolic syndrome, a constellation of cardiometabolic risk factors associated with reduced insulin sensitivity. Using a sensitive direct measurement of insulin resistance as the benchmark to assess the predictive value of different potentially useful clinical markers for insulin resistance in non-diabetic overweight subjects, an elevated TG:HDL-C ratio (> 3.0 mg/dL), compared with an ATPIII diagnosis of metabolic syndrome, has comparable sensitivity (64 vs. 52%) and predictive value (67% vs. 78%) for identifying individuals in the top tertile of insulin resistance (McLaughlin et al., 2003).

Despite the importance of serum lipids for cardiovascular risk prediction, the majority of controlled studies in patients with schizophrenia published to date, including randomized clinical trials such as CATIE, have not included comprehensive measurements of lipid profiles that would allow calculation of non-HDL-C, and no controlled, prospective randomized study data has been reported on changes in non-HDL-C during antipsychotic treatment.

Aripiprazole is an atypical antipsychotic with partial agonism at D₂ dopamine and 5HT_{1A} serotonin receptors and antagonism at 5HT_{2A} serotonin receptors, with a low potential for weight gain, hyperglycemia or adverse effects on any reported lipid components (ADA/

APA/AACE/NAASO, 2004; Burris et al., 2002; Jordan et al., 2002; Keck and McElroy, 2003; Newcomer J. W., 2005; Shapiro et al., 2003). Olanzapine is an atypical antipsychotic with antagonist activity at D₂ dopamine, 5HT_{2A} and 5HT_{2c} serotonin, M1 muscarinic, and H1 histamine receptors, associated with higher risk for weight gain, hyperglycemia and adverse effects on risk-related components of the lipid profile (ADA/APA/AACE/NAASO, 2004; Citrome, 2007; Lieberman et al., 2005; Newcomer J. W., 2005). This study aimed to characterize changes in non-HDL-C and TG:HDL-C that occur during randomized treatment with olanzapine or aripiprazole with a *post-hoc* analysis of pooled data from three randomized, long-term clinical studies in patients with schizophrenia (Chrzanowski et al., 2006; Fleischhacker et al., 2008; McQuade et al., 2004)

2. Methods

2.1 Study design

This *post-hoc* analysis was conducted using pooled data from three multicenter, randomized, long-term (26- or 52-week) studies that investigated the efficacy and tolerability of olanzapine compared with aripiprazole in patients with schizophrenia. Two of the studies were double-blind (Studies CN138-002 (McQuade et al., 2004) and CN138-003 (Fleischhacker et al., 2008) and the third was a 52-week open-label extension to a 26-week, double-blind study (Study CN138-047ext (Chrzanowski et al., 2006)). Details of the three studies are summarized in Table 1. Studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP). Written, informed consent was obtained from every patient or their legal representative.

2.2 Patients

Patients with schizophrenia aged at least 18 years were included in the analysis. Patients had either chronic stable schizophrenia or were in acute relapse and/or required hospitalization (Table 1). Patients with insufficient fasting laboratory data to define baseline or endpoint values of non-HDL-C were excluded from the analysis.

2.3 Study treatments

Olanzapine was administered at doses of 5–20 mg once daily (McQuade et al., 2004) or 10–20 mg once daily (Chrzanowski et al., 2006; Fleischhacker et al., 2008), with a recommended starting dose of 10 mg/day. Aripiprazole was administered at doses of 15–30 mg once daily, with a recommended starting dose of 15 mg/day. In general, concomitant treatment with benzodiazepines and anticholinergic agents was allowed where necessary.

2.4 Assessments

The current analysis assessed the change from baseline in non-HDL-C levels and TG:HDL-C ratios at 26 weeks, using pooled data from all three studies (Chrzanowski et al., 2006; Fleischhacker et al., 2008; McQuade et al., 2004). The change in non-HDL-C levels and TG:HDL-C ratios at 52 weeks was also assessed, using pooled data from the two longer studies only (Chrzanowski et al., 2006; Fleischhacker et al., 2008). Fasting laboratory data were used for the determination of non-HDL-C levels and TG:HDL-C ratios; fasting non-HDL-C was calculated as fasting total cholesterol minus fasting HDL-C.

2.5 Statistical analysis

Change from baseline in non-HDL-C levels and TG:HDL-C ratios was analyzed in the Observed Cases (OC) data set at each time point and in the Last Observation Carried Forward (LOCF) dataset at endpoint. Change from baseline in non-HDL-C levels between

treatment groups was analyzed using analysis of covariance (ANCOVA), with treatment as the main effect and baseline non-HDL-C, age and study protocol as covariates. Gender and duration of exposure to study treatment were insignificant terms in the ANCOVA model at all time points and were therefore excluded from the model.

TG:HDL-C ratios were not normally distributed; thus, nonparametric statistical tests were used for analyses. The signed rank test for medians was used to analyze the change from baseline in TG:HDL-C ratios within treatment groups, and the Kruskal–Wallis test was used to test the differences in median change from baseline in TG:HDL-C ratios between groups.

Mean duration of exposure to study treatments irrespective of dose was also determined.

3. Results

3.1 Patient demographics and baseline characteristics

Of the 1234 patients included in the three original studies (Table 1), a total of 546 patients for whom fasting laboratory data (baseline and at least one post-baseline value of non-HDL-C, HDL-C and TGs) were available were included in the *post-hoc* analysis: 274 in the olanzapine group and 272 in the aripiprazole group. Patient demographics and baseline characteristics were similar for olanzapine and aripiprazole groups (Table 2). Overall, the majority (82.2%) of patients were white, the mean age was 37.9 years and the mean weight was 77.9 kg.

The mean ($\pm$ standard deviation [SD]) duration of exposure to study treatment was 222 ± 142 days for the olanzapine group and 184 ± 146 days for the aripiprazole group. Duration of exposure to study treatment was an insignificant term in the ANCOVA model at all time points and, therefore, mean change from baseline in non-HDL-C levels was not adjusted for duration of exposure.

3.2 Lipid parameters

Mean non-HDL-C levels were similar at baseline with olanzapine and aripiprazole (Table 3). Mean non-HDL-C levels were higher in patients treated with olanzapine than in those treated with aripiprazole at Weeks 26 and 52 (Table 3; OC analyses) and at the LOCF endpoint (mean $\pm$ SE: 153.5 ± 1.93 mg/dL with olanzapine vs. 134.6 ± 1.94 mg/dL with aripiprazole; $p < 0.0001$). There were significant differences between olanzapine and aripiprazole groups with respect to the mean change from baseline in non-HDL-C levels at all time points in the OC data set (Figure 1A) and at the LOCF endpoint (mean $\pm$ SE change: $+9.39 \pm 1.90$ mg/dL with olanzapine vs. -9.30 ± 1.92 mg/dL with aripiprazole; $p < 0.0001$; ANCOVA with treatment as main effect and baseline non-HDL-C, age and study protocol as covariates).

Using a definition of “normal” non-HDL-C levels as those ≤ 130 mg/dL, non-HDL-C levels were in the normal range at baseline but abnormal at Week 52 for 15% of olanzapine- and 6% of aripiprazole-treated patients (Table 4). Non-HDL-C levels were abnormal at baseline and normal at Week 52 in 7% of olanzapine- and 19% of aripiprazole-treated patients (Table 4).

At baseline, median TG:HDL-C ratios for patients randomized to olanzapine and to aripiprazole were not significantly different ($p = 0.84$; Kruskal–Wallis test). It has been suggested that a TG:HDL-C ratio of ≥ 3.5 may be relevant for identifying insulin resistance (McLaughlin et al., 2005); by these standards, baseline TG:HDL-C ratios in olanzapine and aripiprazole groups were high (Table 3). In the olanzapine group, there were no significant changes from baseline in the median TG:HDL-C ratio (Week 6, $p = 0.22$; Week 12, $p = 0.33$;

Week 26, $p=0.06$; Week 52, $p=0.12$; Signed Rank Test for Medians). In the aripiprazole group, the median TG:HDL-C ratio decreased significantly from the baseline value at Week 6 ($p=0.0005$), Week 12 ($p=0.013$), Week 26 ($p=0.0002$) and Week 52 ($p=0.007$; Signed Rank Test for Medians). Significant differences in the median change from baseline in TG:HDL-C ratios were observed with olanzapine versus aripiprazole at all time points in the OC data set (Figure 1B) and at the LOCF endpoint ($+0.10$ vs. -0.29 ; $p<0.0001$; Kruskal–Wallis test). At Week 52, mean TG:HDL-C ratios were 4.18 with olanzapine and 3.07 with aripiprazole (OC data set; Table 3).

Using a definition of “normal” TG:HDL-C ratios as those <3.5 , TG:HDL-C ratios were in the normal range at baseline but abnormal at Week 52 for 15% of olanzapine- and 6% of aripiprazole-treated patients (Table 4). TG:HDL-C ratios were abnormal at baseline and normal at Week 52 in 11% of olanzapine- and 19% of aripiprazole-treated patients (Table 4).

4. Discussion

The results of this analysis provide the first randomized clinical-trial-based evidence confirming that treatment with different antipsychotic medications over 1 year is associated with statistically and clinically significant differences in fasting levels of non-HDL-C, a robust predictor of CVD risk (Farwell et al., 2005; Frontini et al., 2007; Jiang et al., 2004; Liu et al., 2006; Schulze et al., 2004). In this analysis, randomized assignment to aripiprazole treatment was associated with clinically significant reductions in non-HDL-C levels that were rapid in onset and sustained over the year of treatment. Statistically and clinically significant differences in fasting TG:HDL-C ratio, an indicator of insulin resistance as well as CVD risk (Jeppesen et al., 2003; McLaughlin et al., 2005), were also observed with aripiprazole versus olanzapine. Specifically, randomized assignment to aripiprazole treatment was associated with clinically significant improvements in fasting TG:HDL-C that were similarly rapid in onset and sustained over the year of treatment. Furthermore, fewer patients had non-HDL-C or TG:HDL-C levels in the ranges associated with cardiovascular and metabolic risk in the aripiprazole group versus the olanzapine group. The results of these analyses underscore that decisions regarding use of specific antipsychotic medications can significantly influence risk for CVD as well as other insulin resistance-related medical risks. The magnitude of these effects, in a patient population known for substantial cardiometabolic risk and premature CVD mortality (Newcomer J. W. and Hennekens, 2007), is relevant to medical decision-making in patients requiring antipsychotic treatment and needing an intervention to lower non-HDL-C or TG:HDL-C levels (e.g., change in antipsychotic medication versus initiation or increased dose of lipid-lowering pharmacotherapy).

The improvement in non-HDL-C and TG:HDL-C levels during aripiprazole treatment, and worsening or lack of improvement with olanzapine, is consistent with accumulated evidence from other randomized clinical trials as well as other clinical and preclinical evidence regarding medication effects on body weight, total cholesterol and some individual lipid fractions, and plasma glucose levels (ADA/APA/AACE/NAASO, 2004; Newcomer J. W., 2005; Zyprexa, 2008), and also consistent with observed changes in individual, specific lipid fractions from this dataset (L'Italien et al., 2007). Reductions in non-HDL-C and TG:HDL-C during aripiprazole treatment may be best understood as an effect associated with the substitution of aripiprazole for other previous antipsychotic medications that may have been contributing to or supporting the baseline levels of non-HDL-C and TG:HDL-C observed in this analysis, rather than a direct lipid-lowering effect of aripiprazole. This interpretation is consistent with the findings from switch studies with ziprasidone, another metabolically low-risk agent, in which metabolic improvements were greatest in those switched from

olanzapine treatment, and minimal for those switched from relatively lower risk, high-potency typical antipsychotics (Weiden et al., 2003; Weiden et al., 2008). The present data are also consistent with the conclusions from a previous exploratory analysis in a prospective long-term, randomized, double-blind study comparing the metabolic effects of olanzapine and aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder previously treated with olanzapine (Newcomer J.W. et al., 2008). In that study, in the cohort of patients previously treated with olanzapine and switched to aripiprazole, improvements in primary endpoints concerning weight and fasting plasma TG, as well as improvement in the exploratory endpoint of non-HDL-C, were observed for patients randomized to switch to aripiprazole versus patients remaining on olanzapine. The improvements in plasma lipids associated with aripiprazole treatment in that study were of rapid onset in comparison to changes in body weight and were sustained over the long-term follow-up (Newcomer J.W. et al., 2008). Additional randomized studies are also ongoing to assess non-HDL-C levels in patients with schizophrenia who either remain on treatment with their current antipsychotic (olanzapine, risperidone or quetiapine) or switch to aripiprazole therapy (Stroup et al., 2007).

The limitations of the current analysis include the *post-hoc* analytic approach pooling data from several randomized clinical trials. Alternatively, the large sample size and use of pooled study samples could be seen as protecting against disparate results from one sample contributing to spurious results, with metabolic effects of the individual agents consistent across the studies involved. The interpretation of the study is also limited by the unselected metabolic risk characteristics of the sample, with mean baseline body weight being somewhat below that of typical US-based samples and subjects not being pre-selected for criterion-level metabolic risk or specific pre-treatment medication conditions. One might hypothesize, along the lines suggested above, that pretreatment with antipsychotic medications having greater adverse effects on metabolic endpoints would amplify the effects observed in this analysis with aripiprazole, whereas pretreatment with medications similar to aripiprazole with low metabolic risk would limit or eliminate the reductions in non-HDL-C or TG:HDL-C observed during a switch to treatment with aripiprazole itself. The lack of detailed information on pretreatment conditions in this sample prevents testing these hypotheses. However, the unselected sample could also be seen as increasing the generalizability of the results, with more obese or otherwise at-risk patients potentially having a greater benefit of the observed treatment effects.

5. Conclusions

Long-term aripiprazole treatment is associated with significant improvements in the lipid profiles of patients with schizophrenia compared with no improvement or worsening during olanzapine treatment. The findings of this *post-hoc* analysis highlight the need for consideration of CVD risk when prescribing antipsychotic medications, and the need for close monitoring of patients for metabolic changes during treatment (ADA/APA/AACE/NAASO, 2004).

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References

- ADA/APA/AACE/NAASO. Diabetes Care. Vol. 27. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists North American Association for the Study of Obesity; 2004. Consensus development conference on antipsychotic drugs and obesity and diabetes; p. 596-601.
- Allison BD, Mentore LJ, Heo M, Chandler PL, Cappelleri CJ, Infante CM, Weiden JP. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999; 156(11):1686–1696. [PubMed: 10553730]
- Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, Yocca FD, Molinoff PB. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther*. 2002; 302(1):381–389. [PubMed: 12065741]
- Chrzanowski WK, Marcus RN, Torbeyns A, Nyilas M, McQuade RD. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. *Psychopharmacology (Berl)*. 2006; 189(2):259–266. [PubMed: 17058105]
- Citrome L. Olanzapine: interpreting the label change. *Int J Clin Pract*. 2007; 61(12):1960–1962. [PubMed: 17983436]
- Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006; 3(2):A42. [PubMed: 16539783]
- Fagioli A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. *Bipolar Disord*. 2005; 7(5):424–430. [PubMed: 16176435]
- Farwell WR, Sesso HD, Buring JE, Gaziano JM. Non-high-density lipoprotein cholesterol versus low-density lipoprotein cholesterol as a risk factor for a first nonfatal myocardial infarction. *Am J Cardiol*. 2005; 96(8):1129–1134. [PubMed: 16214451]
- Fleischhacker WW, McQuade RD, Marcus RN, Archibald D, Swanink R, Carson WH. A double-blind, randomized comparative study of aripiprazole and olanzapine in patients with schizophrenia. *Biol Psychiatry*. 2008 In press.
- Frontini MG, Srinivasan SR, Xu JH, Tang R, Bond MG, Berenson G. Utility of non-high-density lipoprotein cholesterol versus other lipoprotein measures in detecting subclinical atherosclerosis in young adults (The Bogalusa Heart Study). *Am J Cardiol*. 2007; 100(1):64–68. [PubMed: 17599442]
- Gardner CD, Winkleby MA, Fortmann SP. Population frequency distribution of non-high-density lipoprotein cholesterol (Third National Health and Nutrition Examination Survey [NHANES III], 1988-1994). *Am J Cardiol*. 2000; 86(3):299–304. [PubMed: 10922437]
- Goff DC, Sullivan L, McEvoy JP, Meyer JM, N HA, Daumit G, Lamberti S, D'Agnostino RB, Stroup TS, Lieberman JA. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE Study and matched controls. *Schizophrenia Research*. 2005; 80(1):45–53. [PubMed: 16198088]
- Grundy SM, Cleeman JI, Merz CNB, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004; 110:227–239. [PubMed: 15249516]
- Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. High triglycerides/low high-density lipoprotein cholesterol, ischemic electrocardiogram changes, and risk of ischemic heart disease. *Am Heart J*. 2003; 145(1):103–108. [PubMed: 12514661]
- Jiang R, Schulze MB, Li T, Rifai N, Stampfer MJ, Rimm EB, Hu FB. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. *Diabetes Care*. 2004; 27(8):1991–1997. [PubMed: 15277429]
- Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT(1A) receptor. *Eur J Pharmacol*. 2002; 441(3):137–140. [PubMed: 12063084]

- Keck PE Jr, McElroy SL. Aripiprazole: a partial dopamine D2 receptor agonist antipsychotic. *Expert Opin Investig Drugs*. 2003; 12(4):655–662.
- Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, Revicki D, Buchanan RW. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. *Arch Gen Psychiatry*. 2002; 59(11):1021–1026. [PubMed: 12418935]
- L'Italien GJ, Casey DE, Kan HJ, Carson WH, Marcus RN. Comparison of metabolic syndrome incidence among schizophrenia patients treated with aripiprazole versus olanzapine or placebo. *J Clin Psychiatry*. 2007; 68(10):1510–1516. [PubMed: 17960964]
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005; 353(12):1209–1223. [PubMed: 16172203]
- Liu J, Sempas CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol*. 2006; 98(10):1363–1368. [PubMed: 17134630]
- McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, Meltzer HY, Hsiao J, Scott Stroup T, Lieberman JA. Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005; 80:19–32. [PubMed: 16137860]
- McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med*. 2003; 139(10):802–809. [PubMed: 14623617]
- McLaughlin T, Reaven G, Abbasi F, Lamendola C, Saad M, Waters D, Simon J, Krauss RM. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? *Am J Cardiol*. 2005; 96(3):399–404. [PubMed: 16054467]
- McQuade RD, Stock E, Marcus R, Jody D, Gharbia NA, Vanveggel S, Archibald D, Carson WH. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry*. 2004; 65(Suppl. 18):47–56. [PubMed: 15600384]
- Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res*. 2004; 70(1):1–17. [PubMed: 15246458]
- Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM, Rosenheck RA, Daumit GL, Hsiao J, Swartz MS, Stroup TS, Lieberman JA. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: Prospective data from phase 1. *Schizophr Res*. 2008
- Morrato EH, Newcomer JW, Allen RR, Valuck RJ. Prevalence of baseline serum glucose and lipid testing in users of second-generation antipsychotic drugs: a retrospective, population-based study of Medicaid claims data. *J Clin Psychiatry*. 2008; 69(2):316–322. [PubMed: 18251625]
- Nasrallah HA. Metabolic findings from the CATIE trial and their relation to tolerability. *CNS Spectr*. 2006; 11(7 Suppl 7):32–39. [PubMed: 16816798]
- Nasrallah HA, Meyer JM, Goff DC, McEvoy JP, Davis SM, Stroup TS, Lieberman JA. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. *Schizophr Res*. 2006; 86(1-3):15–22. [PubMed: 16884895]
- NCEP. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001; 285(19):2486–2497. [PubMed: 11368702]
- Newcomer JW. Metabolic risk during antipsychotic treatment. *Clin Ther*. 2004; 26(12):1936–1946. [PubMed: 15823759]
- Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005; 19(Suppl 1):1–93. [PubMed: 15998156]
- Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. *Jama*. 2007; 298(15):1794–1796. [PubMed: 17940236]

- Newcomer JW, Campos JA, Marcus RN, Breder C, Berman RM, Kerselaers W, l'Italian G, Kaplita S, Carson WH, McQuade RD. A multicenter, randomized, double-blind study of the effects of aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder switched from olanzapine. Manuscript under peer review. 2008
- Sattar N, Williams K, Sniderman AD, D'Agostino R Jr, Haffner SM. Comparison of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with other cardiovascular risk factors in patients with the metabolic syndrome in the Insulin Resistance Atherosclerosis Study. *Circulation*. 2004; 110(17):2687–2693. [PubMed: 15492304]
- Schulze MB, Shai I, Manson JE, Li T, Rifai N, Jiang R, Hu FB. Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes. *Diabetologia*. 2004; 47(12):2129–2136. [PubMed: 15662553]
- Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, Roth BL, Mailman R. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology*. 2003; 28(8):1400–1411. [PubMed: 12784105]
- Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, Perkins DO, Keefe RS, Davis CE, Severe J, Hsiao JK. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006; 163(4):611–622. [PubMed: 16585435]
- Stroup TS, McEvoy JP, Swartz MS, Hamer RM, Perkins DO, Lieberman JA. Comparison of antipsychotics for metabolic problems (CAMP): A NIMH Schizophrenia Trials Network study. *Clinical Schizophrenia & Related Psychoses*. 2007 Apr.:69–72.
- Weiden PJ, Daniel DG, Simpson G, Romano SJ. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *J Clin Psychopharmacol*. 2003; 23(6):595–600. [PubMed: 14624190]
- Weiden PJ, Newcomer JW, Loebel AD, Yang R, Lebovitz HE. Long-Term Changes in Weight and Plasma Lipids during Maintenance Treatment with Ziprasidone. *Neuropsychopharmacology*. 2008; 33(5):985–994. [PubMed: 17637612]
- Zyprexa. Eli Lilly and Company Zyprexa (olanzapine) Prescribing Information. Eli Lilly and Company; Indianapolis, IN, USA: 2008.

A

*p=0.0006; **p<0.0001 versus olanzapine (ANCOVA with treatment included as the main effect, and baseline non-HDL-C value, age and study protocol as covariates).

B

*p=0.019; †p=0.004; ‡p=0.001; **p<0.0001 versus olanzapine (Kruskal–Wallis test)

Figure 1.

(A) Mean $\pm$ standard error change from baseline in non-HDL-C levels and (B) median change from baseline in TG:HDL-C ratios among observed cases in aripiprazole and olanzapine groups at 6, 12, 26 and 52 weeks (Observed Cases at each week).

Evaluations at Week 6 and 12 include pooled studies CN138-002 and CN138-003, evaluations at Week 26 include pooled studies CN138-003 and CN138-047ext, and evaluations at Week 52 include CN138-002, CN138-003 and CN138-047ext.

Non-HDL-C=non-high-density lipoprotein cholesterol; ANCOVA=analysis of covariance; TG:HDL-C=triglyceride:high-density lipoprotein cholesterol ratio

Table 1
Overview of the three clinical studies included in the pooled analysis

Study design	Population	Treatment arms	Summary of results at endpoint	Changes in weight (kg) and lipids (mg/dL)	
			Efficacy		
Study 1: CN138-002 (McQuade et al., 2004). 26-week, randomized, double-blind, multicenter, multinational study. Study period: 14 April 2000 – 27 June 2001.	Patients with schizophrenia who were in acute relapse and required hospitalization who had had a previous response to an antipsychotic other than clozapine and been treated as an outpatient for 1 continuous 3-month period in the last 12 months. Patients with CGI-I score 4 (no change/worsening) at Week 6 were discontinued.	Aripiprazole 15–30 mg/day (n=156)Olanzapine 10–20 mg/day (n=161)	<ul style="list-style-type: none"> Completed the study: olanzapine 30%; aripiprazole 25% Mean CGI-I, responder rates and improvements in PANSS Total scores were comparable between groups 	<ul style="list-style-type: none"> Weight: olanzapine +4.23; aripiprazole -1.37 (p<0.001) TG: olanzapine +79.4; aripiprazole +6.5 (p<0.05) HDL-C: olanzapine -3.39; aripiprazole +3.61 (p<0.05) TC: olanzapine +16.3; aripiprazole -1.13 (p=NS) LDL-C: olanzapine +2.27; aripiprazole -3.86 (p=NS) 	
Study 2: CN138-003 (Fleischacker et al., 2008). 52-week, randomized, double-blind, multicenter, multinational study. Acute phase (6 weeks) followed by outpatient phase (46 weeks). Study period: 05 June 2000 – 06 May 2002	Patients with acute schizophrenia who had had a previous response to an antipsychotic other than clozapine and been treated as an outpatient for 1 continuous 3-month period in the last 12 months. Continuation beyond acute phase was dependent on a 1–3-point reduction in CGI score or 20% reduction in PANSS Total score at Week 6.	Aripiprazole 15–30 mg/day (n=355)Olanzapine 10–20 mg/day (n=348)	<ul style="list-style-type: none"> Completed the study: olanzapine 47%; aripiprazole 39% Greater differences in mean changes in PANSS Total scores with olanzapine vs. aripiprazole (LOCF) 	<ul style="list-style-type: none"> TG: olanzapine +10.5 aripiprazole -25.2 (p=0.003) HDL-C: olanzapine +4.8; aripiprazole +5.4 (p=0.692) TC: olanzapine +5.8; aripiprazole -17.0 (p<0.001) LDL-C: olanzapine +2.2; aripiprazole -17.0 (p<0.001) 	
Study 3: 047 extension (Chrzanowski et al., 2006). 52-week, randomized, open-label extension study to a 26-week randomized, double-blind placebo-controlled multicenter, multinational trial. Study period: 22 February 2001 – 19 December 2002.	Patients with schizophrenia. Chronic stable patients: eligible if they completed the double-blind trial. Acutely psychotic patients: eligible if they met relapse criteria and had completed 2 weeks of double-blind therapy.	Aripiprazole 15–30 mg/day (n=104)Olanzapine 5–20 mg/day (n=110)	<ul style="list-style-type: none"> Completed the study: olanzapine 74%; aripiprazole 63% Mean reductions in PANSS Total scores (OC) were similar between groups 	<ul style="list-style-type: none"> Weight: olanzapine +2.54; aripiprazole +0.04 (p<0.001) TG: p=NS between groups HDL-C: a slight worsening with olanzapine vs. a small improvement with aripiprazole (p<0.05) TC: significantly greater increase with olanzapine vs. aripiprazole (p<0.001) LDL-C: worsening with olanzapine vs. improvement with aripiprazole (p<0.001) 	

Of the 1234 patients included in these three studies, fasting laboratory data to define baseline and at least one post-baseline value of non-HDL-C, HDL-C and TGs were available for 546 patients (olanzapine, N=274; aripiprazole, N=272) who were included in the current *post-hoc* analysis.

Concomitant medications not permitted in Studies 1 and 2: haloperidol, fluphenazine, carbamazepine, valproate, fluoxetine, lithium; weight control drugs; beta blockers for akathisia; antihistamines for agitation or anxiety; anticholinergics for EPS at doses equivalent to >6 mg/day benztropine; lorazepam within 4 hours of safety or efficacy assessments. Concomitant medications not permitted in Study 3: antipsychotics other than study medication; investigational agents. Use of concomitant medications: comparable between groups in Studies 1 and 3. In Study 2, more patients received anticholinergics (16 vs. 9%) and hypnotics / sedatives (9 vs. 5%) with aripiprazole vs. olanzapine.

CGI-I=Clinical Global Impressions-Improvement; EPS=extrapyramidal symptoms; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; LOCF=last observation carried forward; NS=not significant; OC=observed case; PANSS=Positive and Negative Syndrome Scale; TC=total cholesterol; TG=triglyceride.

Table 2

Patient demographics and baseline characteristics

	Pooled data used in the <i>post-hoc</i> analysis		
	Olanzapine (N=274)	Aripiprazole (N=272)	Total (N=546)
Mean age (years)	37.9	37.9	37.9
Sex, n (%)			
Male	153 (56)	161 (59)	314 (58)
Female	121 (44)	111 (41)	232 (42)
Race, n (%)			
White	232 (85)	217 (80)	449 (82)
Black	22 (8)	25 (9)	47 (9)
Other	20 (7)	30 (11)	50 (9)
Mean weight (kg)	77.1	78.6	77.9
Mean BMI (kg/m ²)	26.6	27.0	26.8
Mean (SD) baseline lipid values (mg/dL)			
HDL-C	45 (13)	44 (12)	44 (12)
TG	147 (99)	144 (84)	146 (92)
Non-HDL-C	146 (44)	144 (42)	145 (43)
Total cholesterol	190 (45)	188 (41)	189 (43)
TG:HDL-C	3.73 (3.04)	3.79 (2.95)	3.76 (3.00)
LDL-C	116 ± 38	115 ± 37	116 ± 37
Mean (SD) baseline glucose level (mg/dL)	96 ± 22	95 ± 17	95 ± 20

95%CI=95% confidence interval; SD=standard deviation; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; Non-HDL-C=non-high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol

Non-HDL-C levels and TG:HDL-C ratios at baseline and at Weeks 26 and 52 in patients randomized to aripiprazole or olanzapine (Observed Cases data set).

Table 3

Time point	Olanzapine		Aripiprazole	
	N	Mean (SD)	N	Mean (SD)
Non-HDL-C, mg/dL				
Baseline	274	145.7 (44.0)	272	144.0 (41.5)
Week 26 ^a	134	158.0 (44.6)	108	132.4 (39.2)
Week 52 ^b	101	161.4 (48.1)	80	134.6 (42.6)
TG:HDL-C ratio				
Baseline	274	3.73 (3.04)	272	3.79 (2.95)
Week 26 ^a	134	4.02 (3.03)	108	3.03 (2.88)
Week 52 ^b	101	4.18 (3.76)	80	3.07 (2.84)

Non-HDL-C=non-high-density lipoprotein cholesterol; TG=triglyceride

^aPooled studies CN138-002, CN138-003 and CN138-047ext

^bPooled studies CN138-003 and CN138-047ext

Table 4

Changes in the numbers of patients classified with normal or abnormal levels of non-HDL-C or TG:HDL-C at baseline and endpoint. Normal levels of non-HDL-C were defined as 130 mg/dL. Normal levels of TG:HDL-C were defined as <3.5. Normal levels of LDL-C were defined as 100 mg/dL.

Patients n (%)	Olanzapine (N=274)		Aripiprazole (N=272)	
	Patients within the "normal" category at Week 52	Patients within the "abnormal" category at Week 52	Patients within the "normal" category at Week 52	Patients within the "abnormal" category at Week 52
Non-HDL-C				
Patients in the "normal" category at baseline	71 (26)	41 (15)	90 (33)	16 (6)
Patients in the "abnormal" category at baseline	19 (7)	143 (52)	53 (19)	113 (42)
TG:HDL-C ratio				
Patients in the "normal" category at baseline	127 (46)	41 (15)	142 (52)	16 (6)
Patients in the "abnormal" category at baseline	30 (11)	76 (28)	51 (19)	63 (23)

Non-HDL-C=non-high-density lipoprotein cholesterol; TG:HDL-C=triglyceride:high-density lipoprotein cholesterol ratio